Does Stress Management Have a Role in Cardiac **Rehabilitation?**

James A. Blumenthal, Ph.D. Duke University Medical Center Durham, NC USA

35th Annual North Carolina Cardiopulmonary Rehabilitation Symposium Chapel Hill, North Carolina March 14, 2014

Disclosure Information

No Conflicts of Interest





Key Components of Cardiac Rehabilitation

- Evaluation of cardiac status
- Medication management
- Exercise training
- Nutritional counseling
- Smoking cessation
- Vocational counseling
- Stress management?

Outline of Presentation

- Stress
- Definition
- Measurement
- Stress as a risk factor Stress Reduction

 - Pharmacologic
- Behavioral Future directions





 According to ABC News, "it's hard to prove a direct cause-and-effect link. The American Heart Association lists stress as a possible risk factor for heart attacks."

"It's hard to know," said doctors.

- "The reason that the [AHA] and others have not made depression and stress a risk factor for death after myocardial infarction is that the whole concept of stress is very hard to define."
- "What is stressful for one person may not be stressful for another person."

Dr. Brian Olshansky <u>Director of cardia</u>c electrophysiology, University of Iowa Hospitals

Stress and Heart Disease

- "I don't buy the 'stress causes heart disease' paradigm. Our species is well adapted to deal with stress, and most of us don't die suddenly when life gets complicated."
- Dr. Steven Nissen, President of the American College of Cardiology July 16, 2006 as reported in ABC News

Why the Skepticism? **Difficulties in Studying** Stress-CHD Relationship

- No consensus definition of stress
- No "gold standard" for measuring stress
- · No established treatment
- · Not clear when to intervene
- What are appropriate endpoints?

llenges of Atherosclerotic Disease for Behavioral Medicine Research ressive Pathology, Multiple Causes, and Varied Disease Manifestation ors/ Preclinical CAD Ische a/Angina Chronic, long time frame Acute, possible triggered events





Problems with Stress as a Risk Factor

- · How to define it?
- No universal definition
 "Stimulus" or "Response"
 What is "stressful" for one person may not be stressful for another
- How to measure it? – No "gold standard"
 - Many questionnaires
- Biologic markers
- What to do about it?
- dications Behavior change

How to Define Stress?



Stress: Many Definitions

- Some generally accepted facts about stress. Involves triggering stimulus (e.g., war, injury, family, job, finances, etc)
- Has effects on physiology, psychology, and/or behavior
- Some definitions emphasize stimulus, others the outcomes
- Thoughts and perceptions ("appraisals") can increase or decrease stress



Definition of Stress

- Stress in a *process* in which environmental or psychological events, called stressors, come to threaten an person's safety and well-being.
- State of imbalance between *demands* (internal or external) and our ability to **cope** with those demands....
- May be modified by *individual differences* and *contextual factors*

Examples of Individual Differences

- Gender
- Ethnicity
- Personality
- Cardiac status
- Physical fitness











Western Collaborative Group Study

- Prospective cohort study
- >3500 middle aged white males
 Rated as Type A/B based upon SI
- 113 men had CHD initially (80 classified as Type A)
 Followed for ~ 10 yrs (M=8.5 yrs)
 257 developed CHD (178 classified as Type A)



ANDO	ORONARY HI	CART.	DISEASE (CHD)
Musters Octaborative Group Staty	R390 CHD from makin aged new	8 yrs	Structured Interview	Yes
Processingleses Heart Study	1.000 CHD from middle aged men- and weepen	E yes	Freezoghan Type A Scale (and report)	You, in second and white-collar cases
French Belgian Cooperative Heart Study	nam chill dese European teen	S pre.	Seriner Rating Scale field report)	Ter
Belgue Heart Dassas Pre- rentise Trial	LINE CHD-free weakfie-aged Energosaet men	5 ym.	Jeskus Activity Baren Golf reports	Yes
Encurrent Corneary Pre- vention Preport	800 male CHD gataway	5 970	Videotoped Hirsetund Interview	Yes
Multiple Rolk Factor Intervention Trial	10 12,700 high-risk hot CHD-free net 10 3,000 of these men	7 ym.	Jerkini Activity Jay Structured Interview	No No
Multisense Poet-Induction Program	SR male, fomale CHD patients	3 yrs	Jerkins Activity Rep.	No
Aspirix Mysessettal Information Blady	2.300 male, Sensile CMD patients	2.000	Jankins Actienty Bay	No
Honstein Heinrt Franzen	1,399 CHD-free reen	* ym	Jonkins Activity Bay	No

Examples of Contextual Factors

- Environment
- Job Demands/deadlines
- Socio-economic factors
- Social support

Dimensions of Social Support

- Social network
- Size and structure of the network of people available to provide support
- Instrumental/tangible support

 Specific tangible services provided by families and friends

Perceived support

 Subjective evaluation of satisfaction with support







Measuring Stress

- Questionnaires
- Interviews
- Physiological measures
- No "gold standard"

Key Psychosocial Variables in Cardiac Patients: Trait Approach

- Stress
- Depression
- Anger/hostility
- Anxiety

Key Psychosocial Variables in Cardiac Patients: Trait Approach

- Stress
- Depression
- Anger/hostility
- Anxiety

INTERHEART Study

- Yusuf et al. The Lancet, 2004
- Case control study of 15,152 cases (first MIs) and 14, 820 controls from 52 countries.
- More cases than controls reported feeling sad or depressed (OR 1.55).
- Stress was associated with an OR of 1.45.

Psychosocial Stress Measure in INTERHEART Study

- Feeling irritable, anxious, or difficulties with sleeping because of work or home stress
- *Financial stress
- Life events
- Low locus of control
- *Depression (short form CIDI)



Key Psychosocial Variables in Cardiac Patients: Trait Approach

- Stress
- Depression
- Anger/hostility
- Low Social support
- Anxiety

<text><text><text><text><text><text><text></text></text></text></text></text></text></text>	AHA Scien	ce Advisory	
<text><text><text><text><text><text></text></text></text></text></text></text>	Depression and Cor	onary Heart Disease	
<text><text><text><text><text><text><text></text></text></text></text></text></text></text>	Recommendations for Screen	sing, Referral, and Treatment	
<text><text><text><text><text><text></text></text></text></text></text></text>	A Science Advisory From the Ame Committee of the Conneil on Cardio Cardiology, Conneil on Epid Intersplacialing Conneil on Ond	rican Heart Association Prevention vascular Nursting, Connell on Clinical endology and Prevention, and is of Case and Ontroune Research	Circulation
Hart	Endersed by the America	a Psychiatric Americation	Girculation
	Adda H. Ladrinan, 1947, MPH, C. Janus, A. Blarnstathal, 1940, ABPF, Narey T. Fungers, Latprinness, MD, Daniel B, Matt C. Bast Taylor, MD, Erika Strangar Fr	o-Chair, J. Thomas Bigger, Jr. MD. Issuer-Strath, PhD: Peter G. Kastmann, PhD. , MD: M981 David S. Sheye, MD: MS911 solidore, RN: MA, M981, PhD. Co-Chair.	Sept 29, 2008 Vol 118
The starts do loading learning a straight from a "Laboration to the straight from th	Alternet — Depresent a composity proved in periods with with increased conferencedur mechanism and methods. 3 offendly performs this may engine the few merculated as the entralisme histographysics with CHE and periods mittania, and memory of depresents in the CHE and periods.	coverage bear denote CHE-and is subproductly second contract, two for dependence respective devided by applied to the substance. The antidependence of contracts devided in coverage increases devided devices for building of the substance. Science 20, 1999 (2019)	g
	Kay Words: AllA Scientific Streetest # dep	motor a compary factor a provisional factor paired reterency	
The present end of the second barrier of the second barrier of the transmission of the second barrier of the	One of the set of the	denotes the same dependence of the same same same same same same same sam	n, which is further an and the sec
And the second s			a notice a value or

AHA Scientific Advisory

Screening for Depression

Referral for diagnosis and management

Monitor for: adherence to medical care drug efficacy, and safety (CV and mental health)

Coordination of care

Suggest one possible screening tool: PHQ 9

Lichtman et al., Circulation, Oct 2008





- Cohort studies with depression as the exposure and MI or CHD as outcome
- Study design, sample size, depression, outcome, N, Relative Risk abstracted
- 11 studies met inclusion criteria
- RR for the development of CHD was 1.64
- RR for clinical depression was 2.69



tudy sub-category	Relative Risk (random) 95% Cl	Relative Risk (random) 95% Cl
Traditional Risk Factors	1	1.00.00.000
HT Stace 2		1.92 [1.42, 2.59]
smeking	+	1.71 (1.39, 2.10)
labetes		1.47 [1.04, 2.08]
LDL > 160 HDL < 35	+	1.74 [1.36, 2.23]
	199	
Decreased Mont	-	1 49 11 16 1 921
Clinical Depression		2,69 [1.63, 4.43]
02	05 1 2	1
	I not Date High Date	

Depression in Cardiac Patients: **Recent Meta Analyses**

- Barth et al. Psychosom Med 66: 802-813; 2004
- van Melle et al. Psychosom Med 66: 814-822; 2004
- Nicholson et al. European Heart J 27:2763-2774; 2006
- Van der Koy et al. Int J Geriatric Psychiat 22:613-626, 2007

van Melle et al. Psychosom Med 2004

- Scope 1975-2003
- · Articles: 236 publications - 36 met criteria; 22 studies
- Results - All cause: OR 2.38
 - Cardiac: OR 2.59
- Cohort effect: Older studies>more recent studies - OR (<1992)= 3.22 - OR (>1992)= 2.01

Study	Depression mN	No depression mN	GR (96%C) Fixed)	Weight %	OR (95%CI Fixed)
Bush (34)	5/48	12/221		73	212[071,835]
Carney (30)	28/358	11/408		18.8	3.06[1.50,8.24]
inite (18)	15/98	17/203		18.6	1.58[0.94,4.15]
Kaufman (33)	14/87	19/231		17.3	2:14[1:02,4:48]
Leuzon (35)	13/191	15/399	++-	19.3	1.67(0.78,3.60)
Lesperance (32)	8/35	13/187		6.3	3.57(1.50,10.4E)
Meyou (12)	4/26	24/318	++-	6.1	2.23[0.71,8.90]
Shierstone (29)	8/43	1/60		15	11.80(1.42,98.04)
Shik (36)	1/63	4/143		4.8	0.58[0.06,5.12]
Total(95%CI)	96 (952	116/2130		100.0	2.38/1.76,3.22]
Test for heterogeneity chi-s	aure=6.57 dt=8 p=0	58	1400		\sim
Test for overall effect 2=5	59 p<0.00001				
	Notive metal	4	1 4	-	
		Negati	e association Postive assoc	ixtin	

Methods Used in Montreal Studies of Psychosocial Aspects of Acute Coronary Syndromes

- Samples
 - Post-MI: Study I (N=222); Study II (N=678)
 Unstable Angina: Study III (N=430)
 30.8% women; no age limits
- Baseline psychosocial interviews during admission (depression, anxiety, anger, social support) Primary measure of depression: the Beck Depression Inventory

- Usual care · 5-year follow-up for events
- Frasure-Smith, Lespérance, and colle

Sample Items from Beck Depression Inventory (BDI ≥ 10 at least mild to moderate symptoms)

- 1. 0 I do not feel sad.
 - 1 I feel sad.2 I am sad all the time and I can't snap out of it.
 - 3 I am so sad or unhappy that I can't stand it.
- 13. 0 I make decisions about as well as before.
 1 I put off making decisions more than I used to.
 2 I have greater difficulty in making decisions than before

 - 3 I can't make decisions at all any more









Alternate Explanations for Prognostic Impact of Depression in CHD

- Impact not explained by cardiac disease severity.
- Impact not explained by age, gender, or other demographic characteristics
- Impact not explained by differential medication use.
- Impact not explained by overlap of cardiac and depressive symptoms (fatigue, sleep difficulties, etc.).

Key Psychosocial Variables in Cardiac Patients: Trait Approach

- Stress
- Depression
- Anger/hostility
- Anxiety



Cook Medley Scale Sample Item Content

- Cynicism
- I think most people would lie to get ahead. Most people inwardly dislike putting themselves out to help other people. ostile Affect
- Hostile Affect There are certain people whom I disilke so much that I am inwardly pleased when they are catching it for something they have done. Some of my family have habits that bother and annoy me very much. Aggressive Responding When someone does me a wrong, I feel I should pay him back if I can, just for the principle of the thing. I have at times had to be rough with people who were rude or annoying. Hostile Attributions

- Thend to be on my guard with people who are somewhat more friendly than I had expected. I commonly wonder what hidden reason another person may have for doing something nice for me.

Williams et al., Psychosom Med, 1980

- 424 patients undergoing diagnostic coronary arteriography for suspected CHD
- Completed Type A interview and Cook Medley scale
- Type A was associated with increased likelihood of significant occlusion
- Among Type A patients, those with scores indicating high hostility carried most of the effect







Barefoot et al. *Psychosom Med*, 1983

- 255 Medical Students
- Retrospectively examined Cook Medley scores
- Followed for 25 years
- Mortality tracked



Key Psychosocial Variables in Cardiac Patients: Trait Approach

- Stress
- Depression
- Anger/hostility
- Anxiety

Anxiety and Risk of Incident Coronary Heart Disease: A Meta-Analysis

- Meta analysis
- 20 studies
- 249,846 persons
- Average follow up 11.2 yrs
- Anxious persons at increased risk of CHD
 HR 1.26 for CHD
 - HR 1.48 for cardiac death
- Anxiety is an independent risk factor for CHD



Phobic Anxiety and Increased Risk of Mortality in Coronary Heart Disease (Watkins et al. Psychosom Med 2010)

- 947 CHD patients undergoing angiography
- Completed Crown-Crisp Phobic anxiety
- Followed for 3 years
- 137 deaths
- Anxiety associated with HR 1.56 for cardiac mortality and 2.02 for sudden cardiac death in women, but not men



Paradigm Shift

- Chronic traits vs. Acute triggers
- Technological advances
- Intermediate endpoints
 - -Myocardial ischemia -Endothelial dysfunction
 - -Heart rate variability

Acute Triggers of Cardiac Events

- Anecdotal reports
- Epidemiological studies
- · Real-world studies
- · Laboratory studies

Fans help save man at football game Sept 15, 2011 Associated Press

- A Notre Dame fan who had a heart attack during last weekend's game at Michigan survived to watch the final touchdowns from a hospital bed, the school said Thursday.
- Leo Staudacher's heart stopped during the second quarter of Saturday night's game at Michigan Stadium, the school said. The 69-year-old Bay City man survived thanks in part to one bystander who performed CPR and others who called for a medical team, which used an automated electric defibrillator on site.
- automated electric centonilator on site. "I saw the last two touchdowns from the ICU unit," Staudacher said. "It was great to witness an amazing match-up between two old rivals at least for the first quarter and half anyway."

Representative Epidemiological Studies: Major Stress

- Gulf War: Meisel et al., Lancet, 1991
- Northridge Earthquake: Leor et al., NEJM, 1996
- September 11th: Sternberg et al. JACC 2004
- Sporting events: World Cup Soccer, Wilbert-Lampen et al. NEJM, 2008







Acute Triggers: Laboratory Studies Mental stress tasks

- Arithmetic – Public Speaking
- Mirror Tracd
- Physiological Measures - Heart rate
- Blood pressure
- Vascular resistance
- Myocardial ischemia



Mental Stressors

- MAT = Mental Arithmetic
 SPH = Public Speaking
- TRC = Mirror Trace
- READ = Reading (control for speaking)
- SI = Structured Interview
- TMI = Transient Myocardial Ischemia



Paradigm Shift

- Chronic traits vs. Acute triggers
- Technological advances
- Intermediate endpoints
- -Myocardial ischemia
- -Endothelial dysfunction
- -Heart rate variability



Paradigm Shift

- Chronic traits vs. Acute triggers
- Technological advances
- Intermediate endpoints
- -Myocardial ischemia
- -Endothelial dysfunction
- -Heart rate variability











Eligibility Criteria

Documented CAD

- Cardiac catheterization

- Cardiac catheterization
 History of MI
 History of PTCA
 History of CABG
 Positive Exercise Test
- EF > 30%
- BP < 200/120 mm Hg







Case-Crossover Technique

- Compares level of emotional arousal during "case" hours to level of emotional arousal during "control" hours
- <u>Case hour</u>: 1-hour period preceding onset of ischemia
- <u>Control hours</u>:
- Primary control data: all non-ischemic hours
 Secondary control data: comparable 1-hour non-ischemic hour on the alternate day















Mental Stress-Induced Ischemia

- Can be provoked in the laboratory in substantial subset (30-70%) of CAD patients
 Also, may be induced by stress during daily life
 Usually silent (asymptomatic)
 Occurs at lower heart rate threshold than standard exercise testing
 Associated with worse prognosis

- · Associated with worse prognosis
- Treatment?





- Meta analysis-Cochrane Review, 2004 by Reese, West, Smith, & Ibrahim
- RCTs of psychological interventions
- 36 trials, 12, 841 patients
- Results
 - Reduction in non-fatal Mls: OR-0.78 - 2 largest trials-negative
- Evidence of publication bias
- · Quality of many studies considered "poor"

Reese et al. Conclusions

- Psychological interventions showed no evidence of effect on total or cardiac mortality
- · Small reductions in anxiety and depression
- Poor quality of trials makes the pooled finding of a reduction of non-fatal MI "insecure."

Select Completed Randomized Trials with Cardiac Patients

- SADHART: Sentratine Avel-depressant heart Attack Randomized Triat
 Multi-site RCT of placebo vs SSRI for post-ACS patients with MDD
 Primary endpoint: A LVEF: Safety and Efficacy trial (JAMA, 2002)
- ENRICHD: Ennancing Recovery in Concern Heart Disease trial
 Multi-site RCT of CBT (with SSR) vs. usual care for post M patients with depression and/or low coolal support
 Primary endpoint: Mortality and Morbidity; Survival trial (JAMA, 2003)
- SMART HEART
 - 3 Group Design (SMT, EX, UC) Primary endpoint: Myocardial ischemia (JAMA, 2005)

SADHART

- Sertraline Anti-depressant heart Attack Randomized Trial
 - -Multi-site RCT of placebo vs SSRI for post-ACS patients with MDD
 - Primary endpoint: ∆ LVEF; Safety and Efficacy trial (JAMA, 2002)





0 0.5 1 1.5 2 2.5	Event	Relative risk (95% Cl
	Total mortality	0.39 (0.08 – 2.00)
	Myocardial Infarction	0.70 (0.23 - 2.17)
•	Stroke	0.49 (0.09 - 2.65)
	Worsened Angina	0.70 (0.36 - 1.32)
	Congestive Heart Failure	0.62 (0.21 – 1.85)
	Composite	0.68 (0.43 - 1.09)

SADHART-CHF

Sertraline against depression and heart disease in chronic heart failure **Randomized Trial**

- Multi-site RCT of placebo vs SSRI for CHF patients with MDD
 Primary endpoint: A HDRS; Composite cardiovascuar status
 Safety and Efficacy trial also examined survival and cardiac events (JACC, 2010)





SADHART-CHF: Survival Results

ENRICHD

Enhancing Recovery in Coronary Heart Disease

 Multi-site RCT of CBT (with SSRI) vs usual care for post MI patients with depression and/or low social support
 Primary endpoint: Mortality and Morbidity; Survival trial (JAMA, 2003)



ENRICHD Study Design

- Randomized, parallel-group clinical trial to compare the efficacy of a psychosocial intervention vs. usual care
- 2,481 post-MI patients with depression or low social support
- Average 3.4 years of follow-up
- Blinded ascertainment of primary endpoint
- · Intention to treat analysis

































Conclusions

- Stress is associated with worse clinical outcomes in patients with CHD
- Reducing stress has been shown to be associated with improved quality of life in many studies
- Stress management associated with improved biomarkers
- But there is limited evidence that stress reduction improves clinical outcomes.

Key Questions

- · What is the optimal stress management approach?
- · Who to target?
- How and where should stress management be delivered?
- Dissemination-how to get the word out?

Current Stress-Intervention Research in Cardiac Patients

ENHANCED trial

- Comparing Exercise-based Cardiac Rehab with Exercise-based CR enhanced by stress management (J Cardiopul Rehab and Prevention, 2010)
- Does SMT provide "added value" over and above traditional exercise-based CR
- Sites
- Duke UNC

